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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MARVICH, MARIA	
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12/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/763,479	MITTAL ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *7 and 75-77* is/are withdrawn from consideration.

5)☒ Claim(s) *6* is/are allowed.

6)☒ Claim(s) *1-4,8-12,15-22,25-34,37,43-47,50-52,56-58,60,61,63-74 and 97-102* is/are rejected.

7)☒ Claim(s) *23 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 November 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-12,15-34, 37, 43-47, 50-54, 56-58, 60, 61, 63-77 and 97-102

DETAILED ACTION

Claims 1-12,15-34, 37, 43-47, 50-54, 56-58, 60, 61, 63-77 and 97-102 are pending. Claims 7 and 75-77 have been withdrawn. This application contains claims 75-77 drawn to an invention nonelected with traverse in the reply filed on 2/22/07. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. and therefore claims 1-6, 8-12, 15-34, 37, 43-47, 50-54, 56-58, 60, 61, 63-75 and 97-102 are under examination.

Claim Objections

It appears that claims 25 and 29 are intended on being dependent on claim 2 and not 1. As well, claim 32 to claim 30.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 8-12, 15-34, 37, 4343-47, 50-54, 56-58, 60, 61, 63-74, 97-102are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the

time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment.**

Claim 1 has been amended recite "a regulated polymerase III expression system (a) a first nucleic acid segment comprising a regulated promoter operably linked to a first polynucleotide sequence encoding a transcription factor; and (b) a second nucleic acid segment comprising a recombinant polymerase III promoter regulated by the transcription factor, wherein the transcription factor increases transcription from a DNA sequence operably linked to the recombinant polymerase III promoter, and wherein the recombinant polymerase III promoter uses RNA Polymerase III for said transcription". Hence, the claim has been amended to recite that the second nucleic acid comprises a regulated polymerase III promoter regulated by the transcription factor. However, the claim has also been amended to recite that the transcription factor increase transcription from a DNA sequence operably linked to the recombinant polymerase III promoter. Hence, the transcription factor the recombinant polymerase III promoter and also increase transcription from a DNA sequence operably linked to the recombinant polymerase. The written description requirement under 35 USC 112, first paragraph may be met by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Applicant is referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov).

The specification teaches "The term " recombinant" is used herein to mean any nucleic acid comprising sequences which are not adjacent in nature". The specification is limited to teaching that a recombinant polIII promoter can be made by operable linkage of polIII promoter with binding sequences fro a transcription factor (see e.g. figure 1). The amendment changes the scope of the claim such that 1) the recombinant polIII promoter must be usable by RNA polymerase III and 2) wherein the transcription factor binding site is operably linked to the recombinant polIII promoter but those structural requirements of the promoter necessary to make it recombinant are unknown. Thirdly, the claim recites that "a DNA sequence" is operably linked from which the transcription factor increase transcription. However, claim 2 recites that the polII promoter (note not recombinant polIII promoter) comprises a binding site that upon binding to results in an increase in transcription. "Possession may not be shown by merely describing how to obtain possession of members of the claimed genus or how to identify their common structural features." *Ex parte Kubin*, 83 USPQ2d 1410, 1417 (Bd. Pat. App. & Int. 2007) citing *University of Rochester*, 358 F.3d at 927, 69 USPQ2d at 1895. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Rather, the specification is directed to a promoter that is produced by operable linkage of a transcription factor regulatory sequence and/or binding site to a polymerase III promoter. The court and the Board have repeatedly held (Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,18 USPQ2d 1016 (CA FC,

1991); Fiers v. Revel, 25 USPQ2d 1601 (CA FC 1993); Fiddes v. Baird, 30 USPQ2d 1481 (BPAI 1993) and Regents of the Univ. Calif. v. Eli Lilly & Co., 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a description of the nucleic acid itself. Claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived.

In this case, the recombinant promoter must be useable by RNA polIII for transcription but can comprise any modification. Hence, applicants claim a genus of promoter that are not described in the specification. Applicants disclosure amounts to a single species of recombinant promoter wherein a polIII promoter is operable linked to a transcription factor binding site. Recitation of a promoter with other modifications such that it is recombinant are unsupported by the disclosure. As well, the recitation of a DNA sequence is only supported by teachings of binding sites for the transcription factor. A SNA sequence can be a large and diverse genus of sequences wherein the specification only teaches sequences that increase transcription as those that function as binding sites. Given the widely divergent nature of such a genus of recombinant polIII promoters, it must be considered that any composition comprising the recited nucleic acids must be empirically determined. In an unpredictable art, the disclosure of one example would represent to the skilled artisan that applicants were not in possession of claimed genus.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 1-4, 8-12, 15-22, 25-34, 37, 43-45, 47, 50-53, 56-58, 60, 61, 63-74 and 97-99 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al (US 2002/0177564; see entire document) in view of Li et al (US 2004/0146858; see entire document). **This is a new rejection necessitated by applicants' amendment.**

The instant claims are drawn to a regulated polymerase III expression system (a) a first nucleic acid segment comprising a regulated promoter operably linked to a first polynucleotide sequence encoding a transcription factor; and (b) a second nucleic acid segment comprising a recombinant polymerase III promoter regulated by the transcription factor, wherein the transcription factor increases transcription from a DNA sequence operably linked to the recombinant polymerase III promoter, and wherein the recombinant polymerase III promoter uses RNA Polymerase III for said transcription.

Evans et al teach a recombinant promoter wherein a polII promoter is operable linked to at least 4 ecdysone response elements. Transcription factors that bind to these response elements are encoded by nucleic acid segments that express the factors under inducible promoter (see e.g. ¶ 147) as recited in claims 1, 2, 4, 11, 19, 30, 31, 33, 37, 60 and 99. The transcription factors comprise RXR and VgEcR (which alternatively can comprise a Gal4 domain) and are encoded by separate nucleic acid sequences and which encode DNA binding domains and transactivating

domain (see e.g. figure 2). Expression by the transcription factor is dependent upon the presence of inducer (i.e. muristerone or ecdysone) as recited in claim 12, 20, 21, 29, 63-74 and 97. Expression of the transcription factors (also known as regulatory proteins) is under control of an inducible promoter such as a tissue specific promoter and other promoters that are developmentally, temporally or cell cycle regulated (see e.g. 0170) as well as promoters that are regulated by inducers as encompassed by claims 15-18 and 28. The vectors comprising these constructs are used in mammals, which encompass cells and non-human organisms (see e.g. ¶ 28 and 43) as recited in claims 8-10. The regulated promoter further expresses a second "element" such as a sequence of a transgene or an enzyme or reporter genes such as luciferase that emit light or fluoresce, transcription factors and cell surface receptors (see e.g. ¶ 27, 36, 41 and figure 3) as recited in claims 43-45, 50 and 100. The vector for expression is pBluescript, which comprises restriction sites downstream of the pol II promoter as recited in claim 57 and 58. As recited in claims 26, 27 and 32 muristerone does not affect binding affinity of RXR to the promoter (see e.g. figure 2).

Li et al teach an RNA polymerase III promoter (a mammalian U6 promoter) operably connected to a tetO site (see e.g. figure 3 and ¶ 120). Furthermore, a tet repressor is under expression of an inducible promoter (see e.g. ¶ 241-242) which inherently is activated in the presence of an inducer as recited in claims 1-4, 11, 25, 28, 29, 30, 31, 33, 34, 37, 60, 63-73, 98 and 99. The vectors comprising these constructs are used therapeutically, which means that cells comprising the vector are found in the organisms that include as demonstrated in the examples, non human organisms as recited in claims 8-10. The recombinant pol III promoter is operably

linked to siRNA as recited in claims 43, 50-52, 56. There are restriction sites downstream of the pol III promoter as illustrated in figure 1-2 and as recited in claim 58.

KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision Exparte Smith -- USPD2d--., slip op. at 20, (BD. Pat. App. & Interfer. June 25, 2007). As well, KSR teaches that it is within the ordinary skill of the art to combine prior art elements according to known methods to yield predictable results. In the instant case, the combination of Evans et al and Li et al demonstrates an attempt to use known techniques to improve similar promoters using skill that was available at the time of filing with well-established methods on well-characterized sequences. Specifically, Evans et al teach that it is within ordinary skill in the art to combine gal4 binding sites with promoter sequences and Li et al teach that it is within ordinary skill in the art to combine polymerase III promoter sequences with operator sequence. Given the teachings of the cited art and the level of skill of the ordinary skilled artisan at the time of the applicant's invention, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claim 46 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al (US 2002/0177564; see entire document) in view of Li et al (US 2004/0146858; see entire document) as applied to claim1-4, 8-12, 15-22, 25-34, 37, 43-45, 47, 50-53, 56-58, 60, 61, 63-74 and 97-99 above, and further in view of Cheng et al (Gene Therapy, 1997, Vol 4, 1013-1022; see entire document). **This is a new rejection necessitated by applicants' amendment.**

Applicants claim a regulated polymerase III expression system comprising a recombinant polymerase III promoter driving expression of a reporter such as GFP.

The teachings of Evans et al are described above and are applied as before except;

Evans et al do not teach use of GFP as a reporter.

Cheng et al teach use of GFP to assess gene transfer and expression in cells. Cheng et al teach that GFP is an important reporter molecule for non-invasively monitoring gene expression and protein localization with in cells, the fluorescence does not require other co-factors and improved GFP molecules have been made such as S65T and RSGFP4 (See bridging paragraph, page 1013-1032).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the reporter as taught by Evans et al in view of Li et al with the GFP as taught by Cheng et al because Evans et al teach that it is within the ordinary skill of the art to express reporter genes from a recombinant promoter and because Cheng et al teach that it is within the ordinary skill of the art to use GFP as a reporter. One would have been motivated to do so in order to receive the expected benefit that GFP is an important reporter molecule for non-invasively monitoring gene expression and protein localization with in cells, the fluorescence does not require other co-factors and improved GFP molecules have been made such as S65T and RSGFP4. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 54, 100, 101 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evans et al (US 2002/0177564; see entire document) in view of Li et al (US 2004/0146858; see entire document) as applied to 1-4, 8-12, 15-22, 25-34, 37, 43-45, 47, 50-53, 56-58, 60, 61, 63-74 and 97-99 above and further in view of Gardner et al (6,841,376; see entire document). **This is a new rejection necessitated by applicants' amendment.**

Applicants claim a regulated polymerase III expression system comprising a recombinant polymerase III promoter driving expression of ribozyme.

The teachings of Evans et al and Li et al are described above and are applied as before except;

Neither teaches an expression system used to express a ribozyme.

Gardner et al teach that existing expressions for use of regulating ribozymes production was available at the time of filing (col 14, line 4-34). Gardner et al further propose an advance of these systems comprising a first nucleic acid sequence comprising an inducible promoter expressing a regulatory protein or transcription factor that regulates a promoter and a second nucleic acid that comprises a second regulatory protein or transcription factor that regulates expression from the first promoter (see e.g. figure 3b). There are at least two nucleic acid segments in the cell encoding regulatory proteins that bind to the regulated promoter as multiple nucleic acid segments are typically added to a cell for expression.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to include in the expression system as taught by Evans et al in view of Li et al the second transcription factor as taught by Gardner et al because Evans et al in view of Li et al

teach that it is within the ordinary skill of the art to from a recombinant promoter t hat is reguatled by transcription factors and because Gardner et al teach that it is within the ordinary skill of the art to encode sequences that regulate the regulated promoter under control of the promoter. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Argument

Applicants' arguments regarding Gardner et al filed 7/28/08 have been considered but are not persuasive. The instant claim 100 is drawn to a second polynucleotide sequence that encodes either a second transcription factor, a transcriptional activator or a transcriptional repressor. In this case, Gardner et al teach a repressor. As well there are two repressors one that regulates the regulated promoter and the second that regulates a second promoter (as in instant claim 101). The system requires in addition, a sequence that encodes an inhibitor of the repressors as well as a sequence that encodes a genetic toggle switch together that allow expression from one promoter or the other (see figure 4). Hence, Gardner et al does read on the instant claims as recited.

Conclusion

Claims 1-4, 8-12, 15-22, 25-34, 37, 43-47, 50-52, 56-58, 60, 61, 63-74 and 97-102 are rejected.

Claim 6 is allowable as the art does not teach a nucleic acid comprising SEQ ID NO:1.

Claims 5, 23 and 24 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Examiner
Art Unit 1633

/Maria B Marvich/

Primary Examiner, Art Unit 1633